

Therapeutic properties of botulinum toxin on chronic anal fissure treatment and the patient factors role

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ABSTRACT

Background: One of the most frequent distressing diseases which causes anal pain and bleeding after defecation is anal fissure. Despite a poorly understood pathogenesis, the internal anal sphincter spasm has been identified to play a central role in pathogenesis. Recently, botulinum toxin is being used increasingly for the treatment of chronic anal fissure to achieve chemical sphincterotomy and reduce internal sphincter tonicity. Based on the heterogeneity among the published studies, we aimed this study to evaluate its healing rate and for recognizing the factors of patients which may affect the outcome. **Subjects and Methods:** In a prospective case series medical research, 106 patients who suffer from chronic anal fissure were treated by botulinum toxin injections. All patients received 30 units of botulinum toxin and were physically examined every week for 2 months. They were evaluated for bleeding, pain, hematoma, thrombosis, infection, incontinence, and healing of the fissure. At the end of the follow-up period, the fissure healing rate and its relation to age, gender, prior topical therapy, duration of symptoms, and the position of the fissure were assessed. **Results:** At the end of the study (8 weeks), the healing rate was 84.9% (90 patients responded to injections). Healing rate was higher in females and in patients who experienced a shorter duration of symptoms before injection. The mean healing time was 4.68 weeks. In addition, patients with one fissure (anterior or posterior) demonstrated higher healing rate and shorter healing time compared to patients with two fissures (anterior and posterior). **Conclusion:** This study demonstrated that botulinum toxin injection is safe and effective for the treatment of chronic anal fissures, with a low complication rate. In addition, the healing rate was higher in females, patients with shorter duration of symptoms, and those with one fissure.

Keywords: Botulinum toxin, chronic anal fissure, healing rate, patient factors

Introduction

Anal fissure (AF) is a longitudinal rupture or an ulcer in the anal canal. It usually causes anal pain when excreting feces, which may occur with or without rectal bleeding.^[1] It is characterized by anal pain and bleeding after defecation.^[2,3] The anal fissure is divided into two categories: acute (superficial) and chronic (intricate).^[1] In spite of the fact that the internal anal sphincter spasm could

play a crucial role in the pathogenesis of the disease, the chronic anal fissure etiology is still controversial.^[4] The incidence of this disease is 1 in 1000 people per year and is diagnosed by taking a patient's history and physical examination.^[5]

Treatment of anal fissures involves decreasing the resting internal sphincter pressure. Traditionally, this has been done by surgical internal sphincterotomy.^[6] In spite of the fact that the rate of the productiveness of this method may be just 5% lower than one hundred, several concerns would be available on the matter of the disturbance risk in the mechanism of continence.^[7] Recently,

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Received: 25-10-2019

Revised: 21-02-2020

Accepted: 03-03-2020

Published: 26-03-2020

Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_944_19

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How to cite this article: Soltany S, Hemmati HR, Toussy JA, Salehi D, Toosi PA. Therapeutic properties of botulinum toxin on chronic anal fissure treatment and the patient factors role. J Family Med Prim Care 2020;9:1562-6.

less invasive treatments such as topical glyceryl trinitrate (GTN), calcium channel antagonists, and botulinum toxin injection have been suggested.^[8]

Botulinum toxin is used to treat a number of disorders characterized by overactive muscle movement, pain disorders, and autonomic dysfunction.^[9] Similarly, botulinum toxin is used to relax the clenching of muscles, including those of the esophagus^[10] or clenching of the anus which can exacerbate anal fissure.^[11]

Botulinum toxin has been introduced as a treatment modality for chronic anal fissure since 1993. It could act as a temporary chemical sphincterotomy and inhibits the neuromuscular transmitter acetylcholine.^[12] However, it could cause a reduction in internal anal sphincter hypertonicity and also provide the possibility of healing anal fissure.^[13]

Although the injection of botulinum toxin has been applied all over the world, a strict suggestion for this procedure of treatment is not precisely clarified yet.^[14] In addition, there is the heterogeneity of fissure healing rates in response to botulinum toxin in the published studies.^[6]

The main objective of this study is to assess the rate of healing and possible complications of applying botulinum toxin injection for the treatment of chronic anal fissure after short-term follow-up. We also aimed to identify any patient factors that may affect a successful outcome.

Subjects and Methods

In this case series prospective study (nonrandom simple sampling), 106 patients with chronic anal fissure during between July 2017 and January 2019 were enrolled. Inclusion criteria include all patients with evidence of a posterior or anterior ulcer with a skin tag, indurated margins, and persistent symptoms including pain and bleeding after defecation, for more than 8 weeks. Exclusion criteria were patients with acute fissures (<6 weeks), anal abscesses or fistula, history of previous anal surgery, symptomatic hemorrhoids, fissures associated with different pathologies such as inflammatory bowel disease, concomitant medication that could interfere with botulinum toxin, such as aminoglycosides, baclofen or diazepam, and pregnant or breastfeeding women.

The local Ethics Committee approved the study protocol. Before reviewing patients' cases, all stages of the study were explained and a consent letter was taken from all subjects. The identities of all patients and patient factors, including age, gender, duration of symptoms, position of anal fissure and details of previous topical therapy, were recorded. Eligible patients underwent treatment with botulinum toxin A (Botox; Allergan, Irvine, CA). Each patient received a total of 30 units administered at three injections sites into the internal sphincter with an insulin syringe, two injections into both sides of the fissure and one at the 9 o'clock

level according to clockwise in the jackknife position. In patients with two fissures (one in the posterior and the other in anterior midline), the injections were done similarly to posterior fissures. No sedation or local anesthesia was used during the procedure. All the patients were advised to eat a high-fiber diet and laxatives.

They were followed up weekly for 2 months. Symptoms were assessed by direct questioning and fissure healing was assessed by clinical examination. The overall information about the healing of fissure, side effects, complications, and related symptoms was collected prospectively. Healing was considered as a successful treatment. Patients with ongoing symptoms or nonhealed fissure after 2 months were offered either further botulinum toxin injections or surgical intervention. We used MedCalc (Version 18.2.1, MedCalc®, ©1993-2018, www.medcalc.org) statistical software for data entry and for analyzing results. Comparison of quantitative variables was performed by T-test (Fisher exact and Mann–Whitney tests if needed), ANOVA (Kruskall–Wallis if needed), and regression analysis (Linear, with calculating Correlation coefficient). For evaluating the relation of qualitative variables, Chi-square test was used. All the tests were considered statistically significant at *P* values less than 0.05.

Results

106 patients, including 26 male and 90 females, were enrolled in the study. The mean age was 38.56 ± 10.63 years. The most common fissure site was posterior (73.6%). 13.2% (14 patients) had anterior fissures and the remainder (13.2%) had two fissures (anterior and posterior). Duration of topical therapy, including sitz bath, diltiazem ointment, and high fiber diet ranged 1 to 8 weeks (mean 2.16 ± 1.02 weeks). At the end of the study (8 weeks), the healing rate was 84.9% (90 patients healed).

The relation between healing rate and patient factors affecting the outcome of botulinum toxin injection is shown in Table 1. There was not any considerable difference in duration of prior topical therapy and age between healed and nonhealed patients. There was a significantly higher healing rate in females, in patients with shorter duration of symptoms, and in patients who had only one fissure in posterior or anterior midline rather than two fissures (posterior and anterior).

The healing time was between 3 to 7 weeks (mean 4.68 ± 1.3 weeks). As shown in Table 2, this time was significantly longer in patients with two fissures. There was no statistical correlation between healing time and other patient factors.

The mean time of symptom relief after injections was 3.44 ± 1.15 weeks for postdefecatory pain and 2.54 ± 0.96 weeks for bleeding.

The only complication of the treatment was mild incontinence observed in 14 patients (13.2%). All of them were females. 10 patients reported incontinence of flatus and 4 women had

incontinence of flatus and soiling. In all cases, incontinence disappeared spontaneously. The mean time of resolving this problem was 4.42 ± 2.53 weeks (at the range of 2–8 weeks). According to Table 3, there was not any statistical correlation between incontinence and age, gender, duration of symptoms, and topical treatment. However, incontinence was considerably higher in patients who suffer from a posterior anal fissure in comparison with patients with anterior fissures or fissures on both sites (anterior and posterior) (7.7% vs. 28.6%).

Discussion

In recent years, treatment of chronic anal fissure has changed from surgical to medical, both sharing the common goal of reducing spasm of the internal anal sphincter.^[12] The standard medical therapy for the treatment of chronic anal fissure is proved to lateral internal sphincterotomy. In spite of the fact that the success rate of this procedure could be over 95%, within the mechanism of continence, there would be a great concern on the disturbance risk.^[7] On the other hand, in spite of the fact that the incontinence risk following the procedure could be about 1%–9%,^[5,15] the incontinence risk following sphincterotomy may be considered to be existing lifelong.^[15]

This concern had led to the increasing use of alternative methods of reducing internal anal sphincter tonicity.^[6] Topical pharmacological treatments, such as nitrates and calcium channel blockers like diltiazem have been proven to be more effective in comparison to placebo. The application of these kinds of therapies could induce resistant side effects like headache for a while.^[16] Given these issues, attention has turned to the use of botulinum toxin.^[6] Since botulinum toxin was introduced as an effective option for treatment of anal fissures, many studies have suggested encouraging results^[8] and although the fissure healing rate is lower than with internal sphincterotomy, the lack of long-term incontinence has prompted suggestions to use the toxin as first-line therapy.^[17]

However, the existing studies are heterogeneous and the reported efficacy for fissure healing appears to be highly variable.^[6,13,17] Karabulut *et al.* have reported healing rates of 80% in patients treated with 25 units botulinum toxin after 2 months follow-up and 90% after second injection. They injected botulinum toxin into the internal anal sphincter.^[2] In another study, 192 patients received botulinum toxin with an average dose of 40 units. Median follow-up was 9 months (Range 2–50 months) and 86.5% of their patients were successfully treated.^[6] Dat *et al.* reported 67% complete resolution anal fissures after 3 months; These patients were given 33 units of botulinum toxin.^[13] In a meta-analysis study conducted by Bobkiewicz *et al.* which include 34 prospective studies, a total of 1577 patients undergo either Dysport or Botox as treatments. The efficiency of analysis through these studies varies at the range of 33%–96%.^[14]

We obtained the healing in 90 patients out of 106 treated with one injection of 30 units of botulinum toxin into the internal

Table 1: Patient factors affecting the healing rate of botulinum toxin injection in chronic anal fissure (in 8-week follow-up period)

Factor	Healed	Nonhealed	P
Age (years)	39±11.01	36.12±8.02	>0.05
Sex			
Female	84 (93.3%)	6 (37.5%)	<0.001
Male	6 (37.5%)	10 (62.5%)	
Duration of Symptoms (months)	7.91±8.06	22.37±38.45	0.001
Duration of topical treatment (weeks)	2.22±1.09	1.87±0.34	>0.05
Fissure site			
Posterior	68 (87.2%)	10 (12.8%)	>0.05 ^a
Anterior	14 (100%)	-	
Posterior and Anterior	8 (57.1%)	6 (42.9%)	0.001 ^b

^aComparison of healing rates in patients with posterior fissures and patients with anterior fissures.

^bComparison of healing rates in patients with one fissure (Posterior or Anterior) and patients with two fissures (Posterior and Anterior)

Table 2: Effect of fissure site on healing time after botulinum toxin injection in chronic anal fissure (in 8-week follow-up period)

Fissure Site	Healing time (weeks)	P
Posterior	4.61±1.31	0.007 ^a
Anterior	4.28±0.91	
Posterior and Anterior	6±1.06	

^aANOVA and Scheffe tests showed a significant difference between the patients with one fissure (posterior or anterior) and patients with two fissures (posterior and anterior)

Table 3: Patient factors affecting the incontinence rate after botulinum toxin injection in chronic anal fissure

Factor/Complication	Incontinence	Without Incontinence	P
Age (years)	40.57±9.49	38.26±10.81	>0.05
Female Sex	14 (15.6%)	-	0.091
Duration of Disease (months)	13±8.8	9.56±18.05	>0.05
Duration of Local treatment (weeks)	2.14±0.36	2.17±1.09	>0.05
ite of Fissure			
Posterior	6 (7.7%)	72 (92.3%)	0.019 ^a
Anterior	4 (28.6%)	10 (71.4%)	0.009 ^b
Posterior and Anterior	4 (28.6%)	10 (71.4%)	

^aComparison of posterior fissures and anterior fissures, and also posterior fissures and simultaneous posterior and anterior fissures. ^bCalculated for trend

anal sphincter. The healing rate after 2-month follow-up was 84.9% with an average healing time of 4.68 weeks.

Similar to the healing rate, the results for average healing time varies between different studies. In one study, the healing with a success rate of 65% happened in 39 patients during a 3-month follow-up of patients with an average healing time of 6.4 weeks, after the 1st injection.^[18] On the other hand, at their study Glover *et al.* through studying 75 patients demonstrated that during 3-month follow-up of patients, a success rate of 90.7% with an average healing time of 6.2 weeks achieved.^[19] In our study, as we mentioned above, average healing time of fissure healing was 4.68 weeks (3 to 7 weeks).

Although the results of our experience were favorably compared to some of the mentioned studies, such varying results in

healing rate and time can be attributed to the differences in patient selection criteria, different techniques of injection, and use of varying dose and injection sites.^[20] Similarly, the bodyweight/dosage ratio may influence the outcome as well. However, this requires further clinical studies.^[2]

The impact of patient factors on the response to botulinum toxin injection is poorly studied.^[6] In the Lindsey *et al.* study, patient factors, including gender, presence of a sentinel pile, duration of symptoms, fissure site, and the previous symptoms did not show a statistically significant effect on fissure healing after botulinum toxin injections.^[21] Abbas and Ahmad reported that patient factors including duration of the disease, type and position of fissure, and prior topical therapy did not significantly influence the response to the toxin. However, they noted a nonsignificant trend of better healing in females and lower duration of symptoms.^[6]

In our study, we assessed the effect of age, gender, fissure position, duration of symptoms, and duration of the previous topical treatment at the healing rate after botulinum toxin injection. Unlike the mentioned study, our study was prospective and the dose, volume, site, and number of injections were the same in all the cases. Age and duration of the previous topical therapy were not significantly associated with improved healing. But, there was a significantly higher healing rate in females and in patients with one fissure. In addition, patients with shorter duration of symptoms showed significantly better response. Therefore, we suggest a botulinum toxin injection in the early course of chronic anal fissure for better response. This is noted in the Brisinda *et al.* study. According to this study, higher healing rates can be achieved if the toxin is given early in the course of the disease and before the chronic fibrosis of the fissure is established.^[22]

The effect of duration of symptoms on the outcome has been considered in some studies. In a study by Karabulut *et al.*, they recommended that botulinum toxin could be applied as an alternative therapy for appropriate treatment of chronic anal fissure among patients whose symptoms persisted less than one year.^[2] At their study, Piccinni *et al.* by investigating the effect of botulinum toxin in the treatment of chronic anal fissure, excluded the fissures that lasted for more than 6 months. They were often associated with large skin tags because of the presence of sclerotic tissue.^[23]

Although some studies did not show the relation between gender and healing, our female patients had a higher healing rate. We administered the same dose of 30 units for all patients. Because of anatomic differences between men and women,^[24] the male patients probably need higher doses for equal response.

In our experience, patients with one fissure (anterior or posterior) compared to patients with two fissures (anterior and posterior) showed higher healing rate and shorter healing time. For patients with two fissures, botulinum toxin was injected with the same

doses and sites as posterior fissures. It could be proposed that patients with two fissures may need different doses or injection sites to achieve a similar healing rate and healing time. This requires further studies.

The results of the studies demonstrate that botulinum toxin injections are associated with low side effects. Transient flatus incontinence and/or fecal incontinence are two of the commonest side effects which could happen in 10% and 5% of cases, respectively.^[15,25] Moreover, in another study, the occurrence rate of flatus incontinence and fecal incontinence was reported to be 0.8% and 4%, respectively. These reported percentages were lower in comparison with other similar studies.^[13] Within a meta-analysis consist of 34 prospective studies, the rate of patients who expanded perianal complications like hematoma, perianal abscess or thrombosis, due to botulinum toxin injection was only 2.2%. Based on the findings of the present study, the overall rate of incontinence was 5.01%. The higher percentage of these patients represented only mucus incontinence or transient flatus which could be resolved spontaneously during the time period of 1–8 weeks. During each session, the overall amount of applied botulinum toxin was at the range of 5–150 IU. Moreover, the results of the present study did not report any correlation among the botulinum toxin dosage and the rate of postoperative incontinence or complications.^[14] On the other hand, the results of another study confirmed that higher doses of botulinum toxin lead to an increase in complications and side effects. The authors proposed that it is probably related to the diffusion of the toxin to the external sphincter. They noticed that the diffusion of botulinum toxin in the tissues is a dose-dependent phenomenon. In our study, none of the patients developed perianal complications. The only complication was mild flatus incontinence or soiling observed in 14 patients (13.2%). In all cases, incontinence disappeared spontaneously (ranged from 2 to 8 weeks). Although all of these patients were females, there was not any significant correlation between complication rate and gender ($P = 0.091$).

Our study was limited by its short follow-up period. Hence, we cannot declare long-term efficacy and recurrence rate following the injection of botulinum toxin.

Conclusion

We concluded that botulinum toxin Botox is a safe and effective modality for the treatment of chronic anal fissure, with a low complication rate. According to our study, it seems that females, patients with shorter duration of symptoms, and those with one fissure show a better response to the treatment.

Acknowledgements

We would like to thanks the Clinical Research Development Unit of Kossar Hospital Educational and Research and Therapeutic Center of Semnan University of Medical Science for providing facilities for this work.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Özdamar MY, Hirik E. Anal fissure epidemiology and related diseases in children. *South Clin Istanbul Eurasia* 2018;29:295-300.
- Karabulut Z, Doğan P, Moray G. Effect of botulinum toxin in selected chronic anal fissure patients: Long-term results. *Prz Gastroenterol* 2012;7:383-5.
- Godevenos D, Pikoulis E, Pavlakis E, Daskalakis P, Stathouloupoulos A, Gavrielatou E, *et al.* The treatment of chronic anal fissure with botulinum toxin. *Acta Chir Belg* 2004;104:577-80.
- Brisinda G, Albanese A, Cadeddu F, Bentivoglio AR, Mabisombi A, Marniga G, *et al.* Botulinum neurotoxin to treat chronic anal fissure: Results of a randomized "Botox vs. Dysport" controlled trial. *Aliment Pharmacol Ther* 2004;19:695-701.
- Ooijsaar RE, Felt-Bersma RJF, Han-Geurts JJ, van Reijn D, Vollebregt PF, Molenaar CBH. Botox treatment in patients with chronic functional anorectal pain: experiences of a tertiary referral proctology clinic. *Tech Coloproctol* 2019;23:239-44.
- Abbas K, Ahmad M. Patient factors do not predict symptomatic response to botulinum toxin for the treatment of anal fissure. *Int Surg J* 2016;3:484-7.
- Barnes TG, Zafrani Z, Abdelrazeq AS. Fissurectomy combined with high-dose botulinum toxin is a safe and effective treatment for chronic anal fissure and a promising alternative to surgical sphincterotomy. *Dis Colon Rectum* 2015;58:967-73.
- Chen HL, Woo XB, Wang HS, Lin YJ, Luo HX, Chen YH, *et al.* Botulinum toxin injection versus lateral internal sphincterotomy for chronic anal fissure: A meta-analysis of randomized control trials. *Tech Coloproctol* 2014;18:693-8.
- Safarpour Y, Jabbari B. Botulinum toxin treatment of movement disorders. *Curr Treat Options Neurol* 2018;20:4.
- Stavropoulos SN, Friedel D, Modayil R, Iqbal S, Grendell JH. Endoscopic approaches to treatment of achalasia. *Therap Adv Gastroenterol* 2013;6:115-35.
- Carter D, Dickman R. The role of botox in colorectal disorders. *Curr Treat Options Gastroenterol* 2018;16:541-7.
- Brisinda G, Cadeddu F, Brandara F, Marniga G, Maria G. Randomized clinical trial comparing botulinum toxin injections with 0.2 per cent nitroglycerin ointment for chronic anal fissure. *Br J Surg* 2007;94:162-7.
- Dat A, Chin M, Skinner S, Farmer C, Wale R, Carne P, *et al.* Botulinum toxin therapy for chronic anal fissures: Where are we at currently? *ANZ J Surg* 2015;87:1-4.
- Bobkiewicz A, Francuzik W, Krokowicz L, Studniarek A, Ledwosiński W, Paszkowski J, *et al.* Botulinum toxin injection for treatment of chronic anal fissure: Is there any dose-dependent efficiency? A meta-analysis. *World J Surg* 2016;40:3064-72.
- Sileri P, Mele A, Stolfi VM, Grande M, Sica G, Gentileschi P, *et al.* Medical and surgical treatment of chronic anal fissure: A prospective study. *J Gastrointest Surg* 2007;11:1541-8.
- Sileri P, Stolfi VM, Franceschilli L, Grande M, Di Giorgio A, D'Ugo S, *et al.* Conservative and surgical treatment of chronic anal fissure: Prospective longer term results. *J Gastrointest Surg* 2010;14:773-80.
- Ravindran P, Chan DL, Ciampa C, George R, Punch G, White SI. High-dose versus low-dose botulinum toxin in anal fissure disease. *Tech Coloproctol* 2017;21:803-8.
- Helmi Ibrahim A, Abd El Aal Sultan A. Management of chronic anal fissure by chemo-denervation of the internal anal sphincter using botulinum toxin A. *AAMJ* 2015;13:189-97.
- Glover PH, Tang SJ, Whittle JZ, Davis ED, Jex KT, Wu R, *et al.* High-dose circumferential chemodenervation of the internal anal sphincter: A new treatment modality for uncomplicated chronic anal fissure: A retrospective cohort study (with video). *Int J Surg* 2015;23:1-4.
- Fruehauf H, Fried M, Wegmueller B, Bauerfeind P, Thumshirn M. Efficacy and safety of botulinum toxin A injection compared with topical nitroglycerin ointment for the treatment of chronic anal fissure: A prospective randomized study. *Am J Gastroenterol* 2006;101:2107-12.
- Lindsey I, Cunningham C, Jones OM, Francis C, Mortensen NJ. Fissurectomy-botulinum toxin; a novel sphincter-sparing procedure for medically resistant chronic anal fissure. *Dis Colon Rectum* 2004;47:1947-52.
- Brisinda G, Maria G, Bentivoglio AR, Cassetta E, Gui D, Albanese A. A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure. *N Engl J Med* 1999;341:65-9.
- Piccinni G, Poli E, Angrisano A, Sciusco A, Testini M. Botox for chronic anal fissure: Is it useful? A clinical experience with mid-term follow-up. *Acta Biomed* 2009;80:238-42.
- Brady JT, Althans AR, Neupane R, Dosokey EM, Jabir MA, Reynolds HL, *et al.* Treatment for anal fissure: Is there a safe option? *Am J Surg* 2017;214:623-8.
- Yiannakopoulou E. Botulinum toxin and anal fissure: Efficacy and safety systematic review. *Int J Colorectal Dis* 2012;27:1-9.